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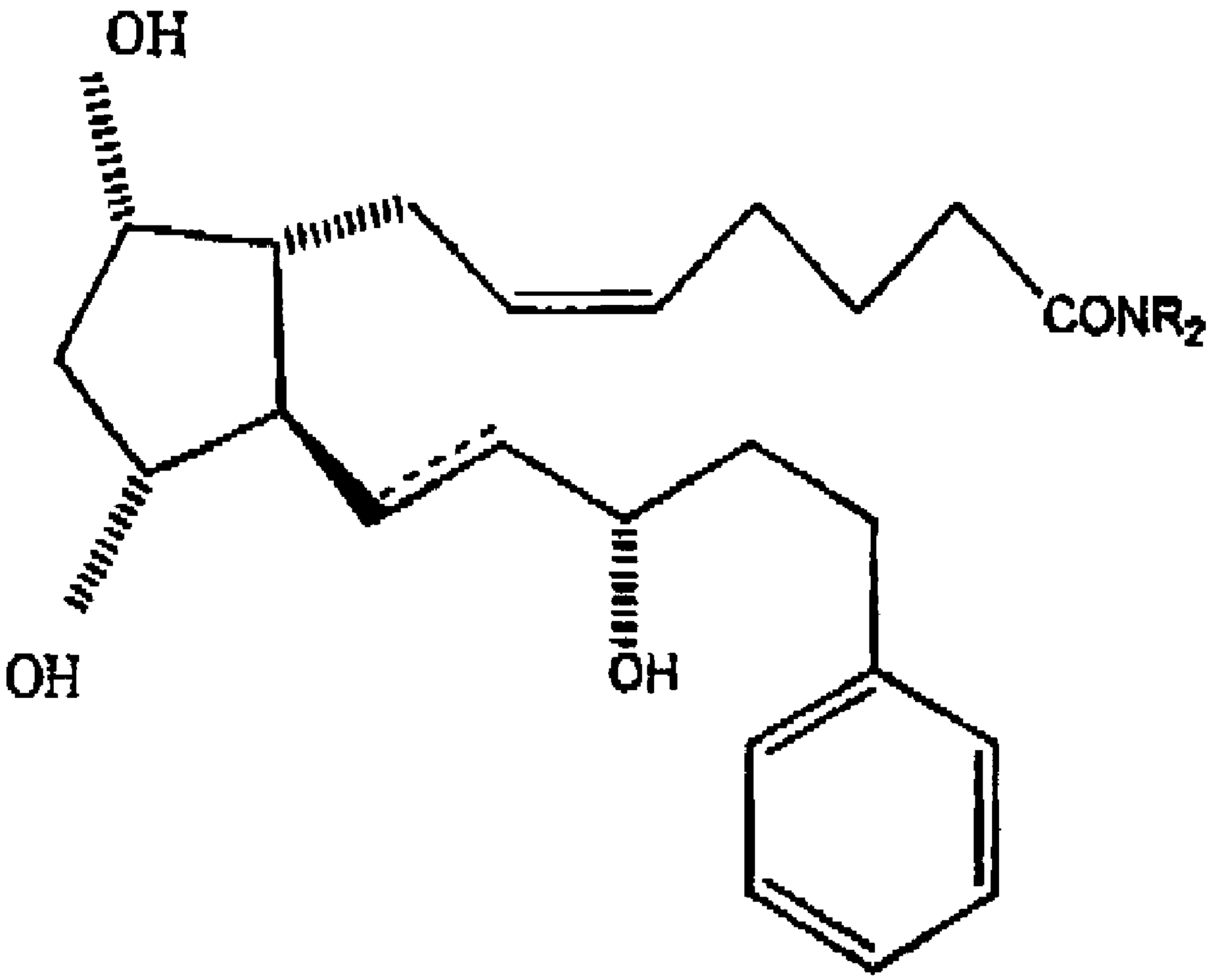
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(54) Titre : PREPARATION DE PROSTAMIDES
(54) Title: PREPARATION OF PROSTAMIDES




(57) Abrégé/Abstract:
The present invention provides a process for the preparation of a prostamide which comprises the steps of (d) reacting first intermediate having the general formula (I) with DIBAL wherein Z is a protecting group and the dotted line represents the presence

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(57) **Abrégé(suite)/Abstract(continued)**:
or absence of a double bond to yield a second intermediate having the general Formula (II) (b) reacting said second intermediate with $Na(TMS)_2N$ and $(C_6H_5)_3P^+(CH_2)_6CONR_2X$ wherein R is a $C_{1-5}$ alkyl or hydrogen and X is an anion to yield a third intermediate having the general formula (III) (c) reacting said third intermediate with a protecting agent to yield a fourth intermediate having the general formula IV (e) reacting said fourth intermediate to remove said protecting groups and yield a prostamide having the general formula V

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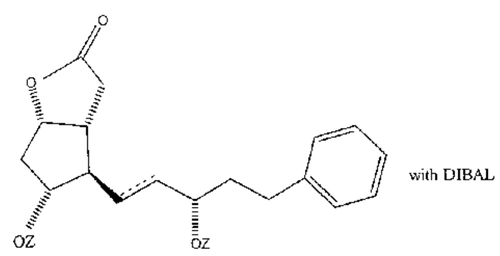
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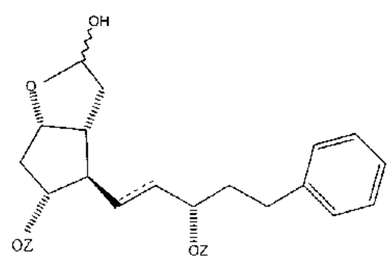
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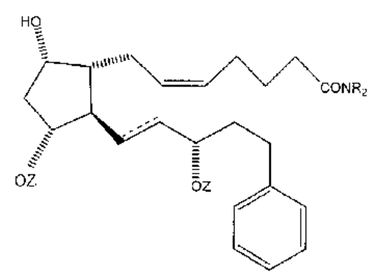
(54) Title: PREPARATION OF PROSTAMIDES



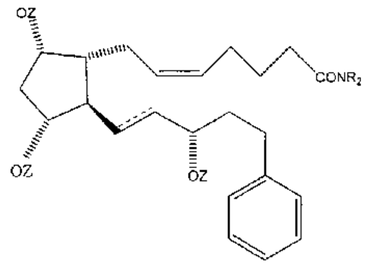

(I)



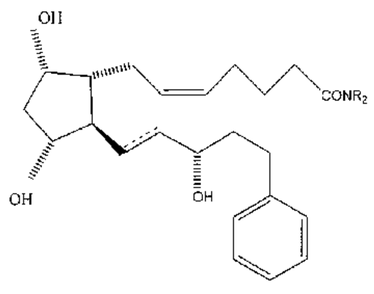

(II)




(III)




(IV)




(V)

**(57) Abstract:** The present invention provides a process for the preparation of a prostamide which comprises the steps of (d) reacting first intermediate having the general formula (I) with DIBAL wherein Z is a protecting group and the dotted line represents the presence or absence of a double bond to yield a second intermediate having the general Formula (II) (b) reacting said second intermediate with $Na(TMS)_2N$ and $(C_6H_5)_3P^+(CH_2)_6CONR_2X$ wherein R is a $C_{1-5}$ alkyl or hydrogen and X is an anion to yield a third intermediate having the general formula (III) (c) reacting said third intermediate with a protecting agent to yield a fourth intermediate having the general formula IV (e) reacting said fourth intermediate to remove said protecting groups and yield a prostamide having the general formula V

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# PREPARATION OF PROSTAMIDES

## BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the synthesis of prostamides, which may be useful as pharmaceutical compounds, e.g. as medicinal compounds useful for treating glaucoma and/or lower elevated intraocular pressure.

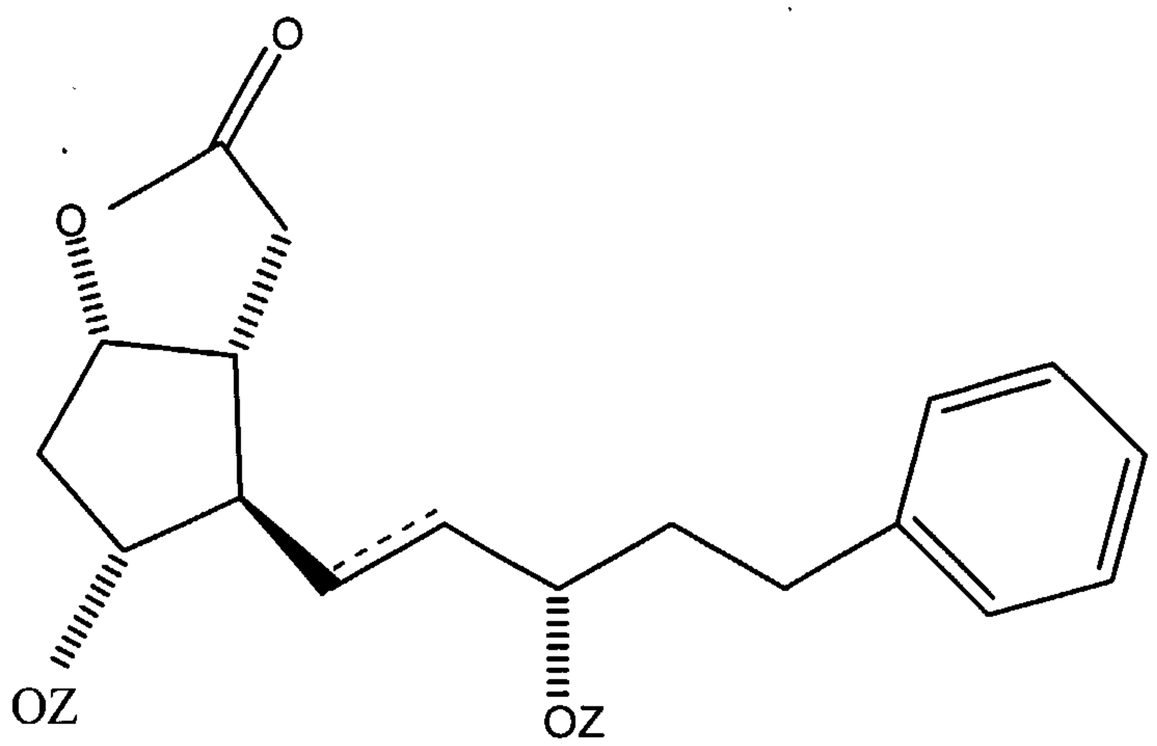
2. Description of Related Art

The prior art teaches the synthesis of various prostamide compounds. For example, U.S. Patent 3, 954,741 to Schaaf et al., and the Journal of Medicinal Chemistry, 1979, Vol. 22, No. 11, pp. 1346 et seq describes the synthesis of N-substituted prostaglandin carboxamides and other intermediates and compounds. Similarly, Gandolfi et al., (U.S. 4,195,183) and PCT Publication WO 0155102 describe the synthesis of other prostamides.

## BRIEF SUMMARY OF THE INVENTION

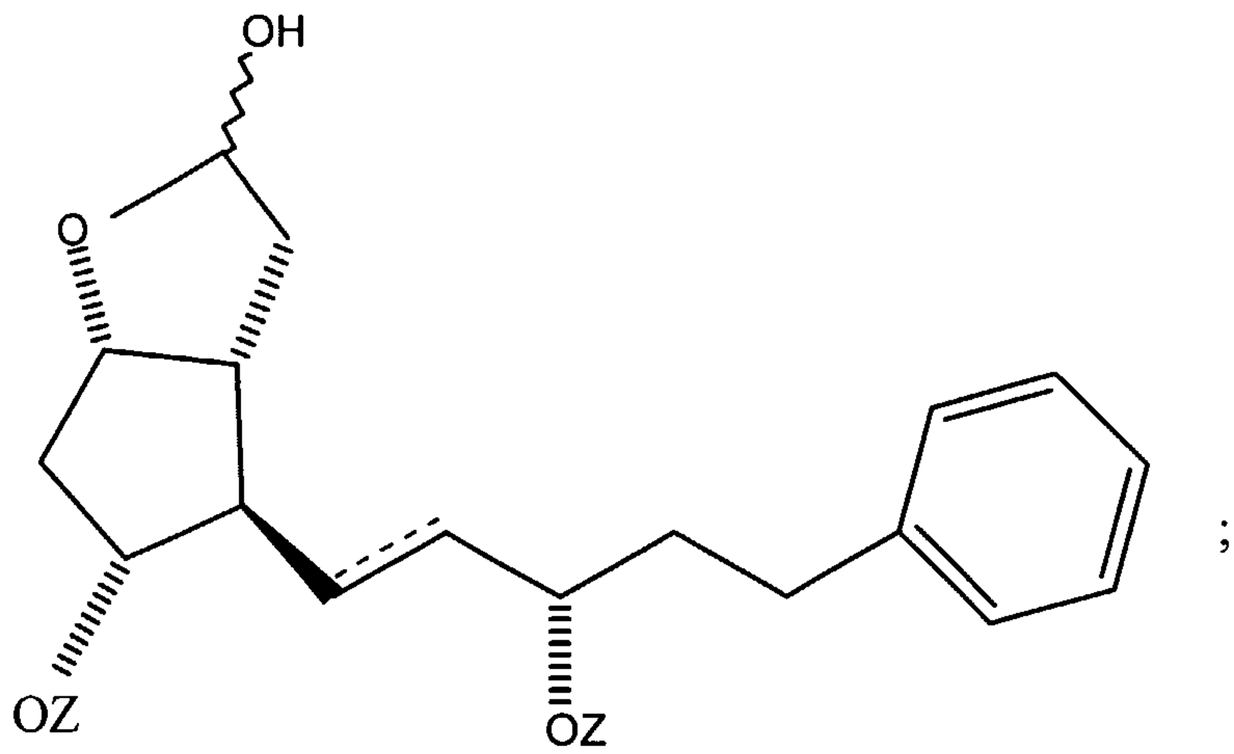
The present invention provides a process for the preparation of a prostamide which comprises the steps of

(a) reacting first intermediate having the general formula I



with DIBAL

wherein Z is a protecting group and the dotted line represents the presence or absence of a double bond to yield a second intermediate having the general Formula II

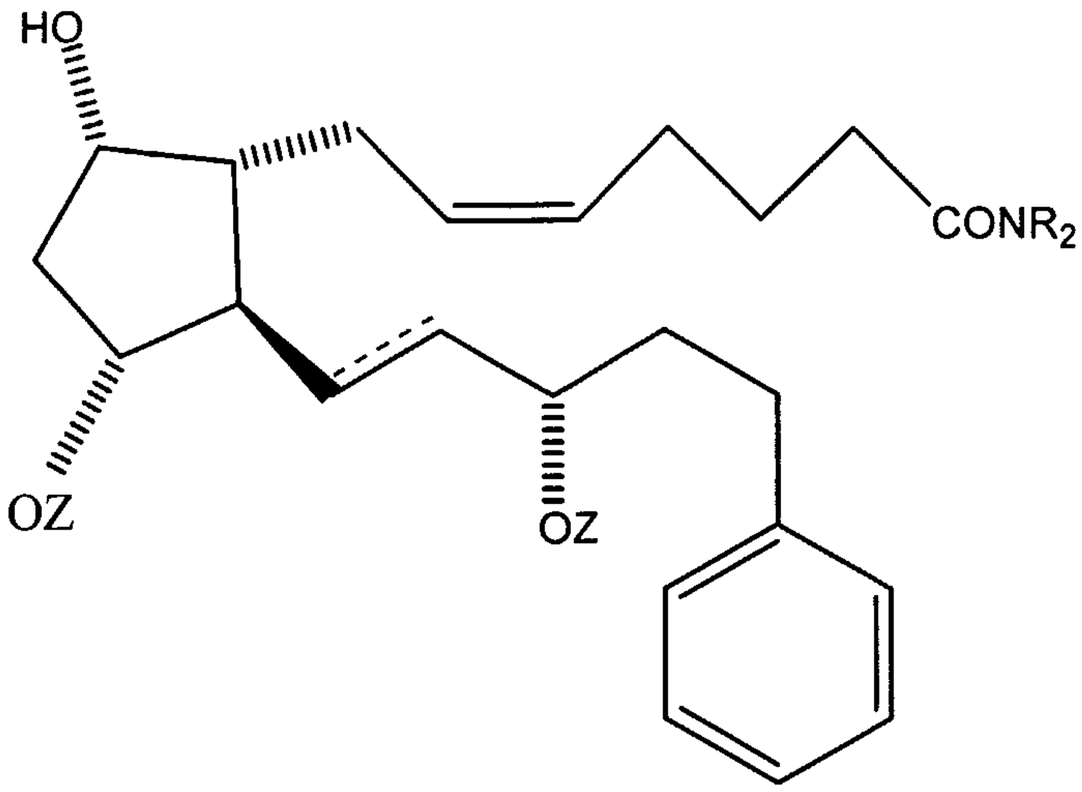


;

(b) reacting said second intermediate with

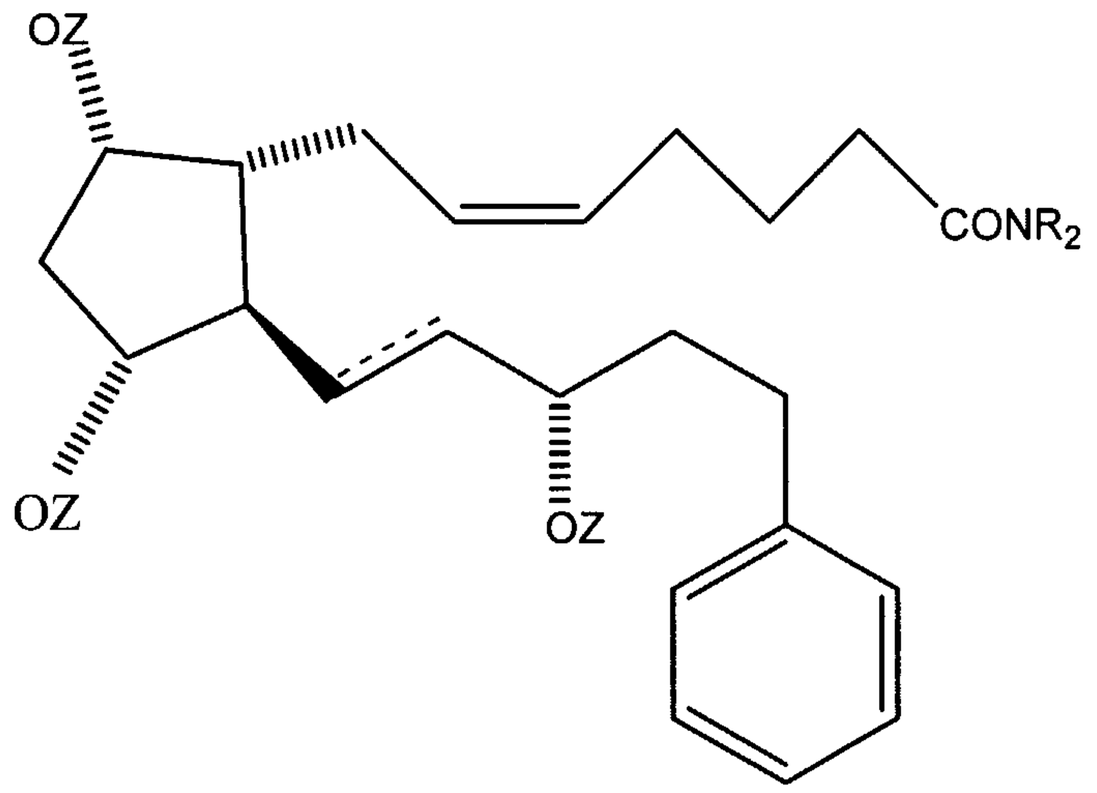
$Na(TMS)_2N$ and $(C_6H_5)_3P^+(CH_2)_6\ CONR_2\ X^-$

wherein R is a $C_1$-$_5$ alkyl or hydrogen and $X^-$ is an anion to yield a third intermediate having the general formula III



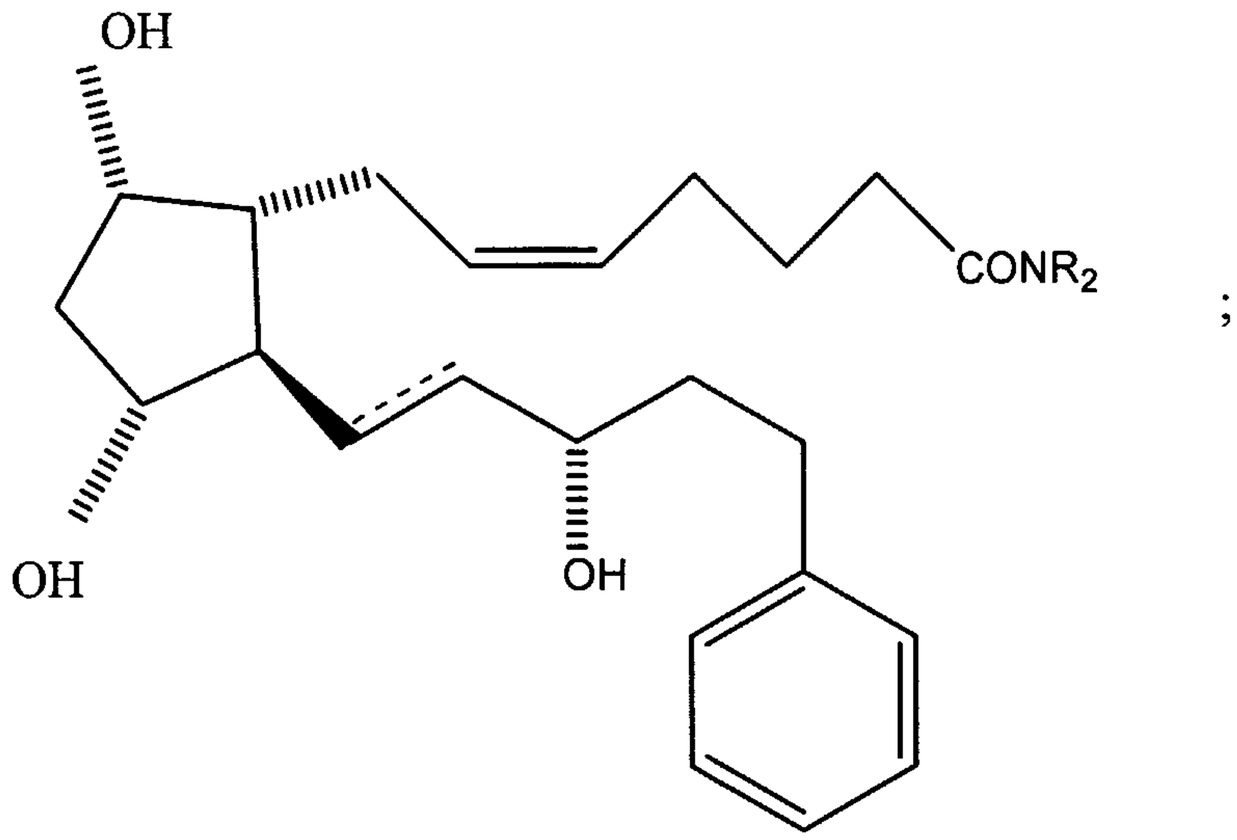

;

(c) reacting said third intermediate with a protecting agent to yield a fourth intermediate having the general formula IV




;

(d) reacting said fourth intermediate to remove said protecting groups and yield a prostamide having the general formula V

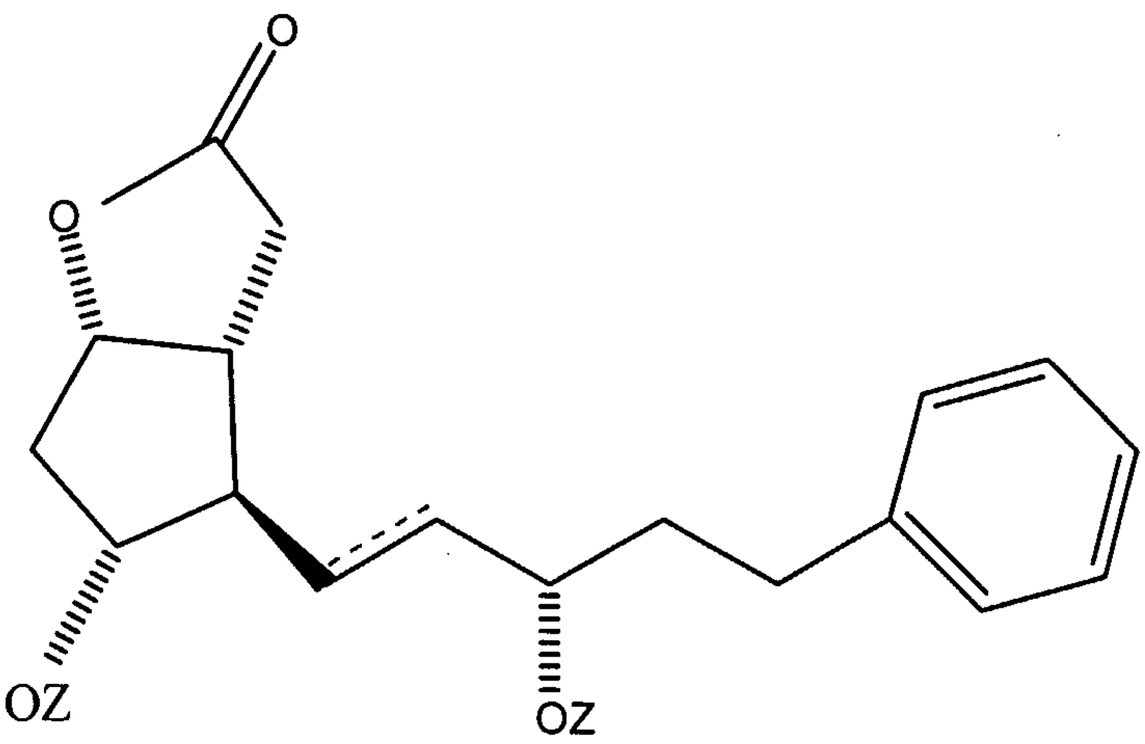



;

## DETAILED DESCRIPTION OF THE INVENTION

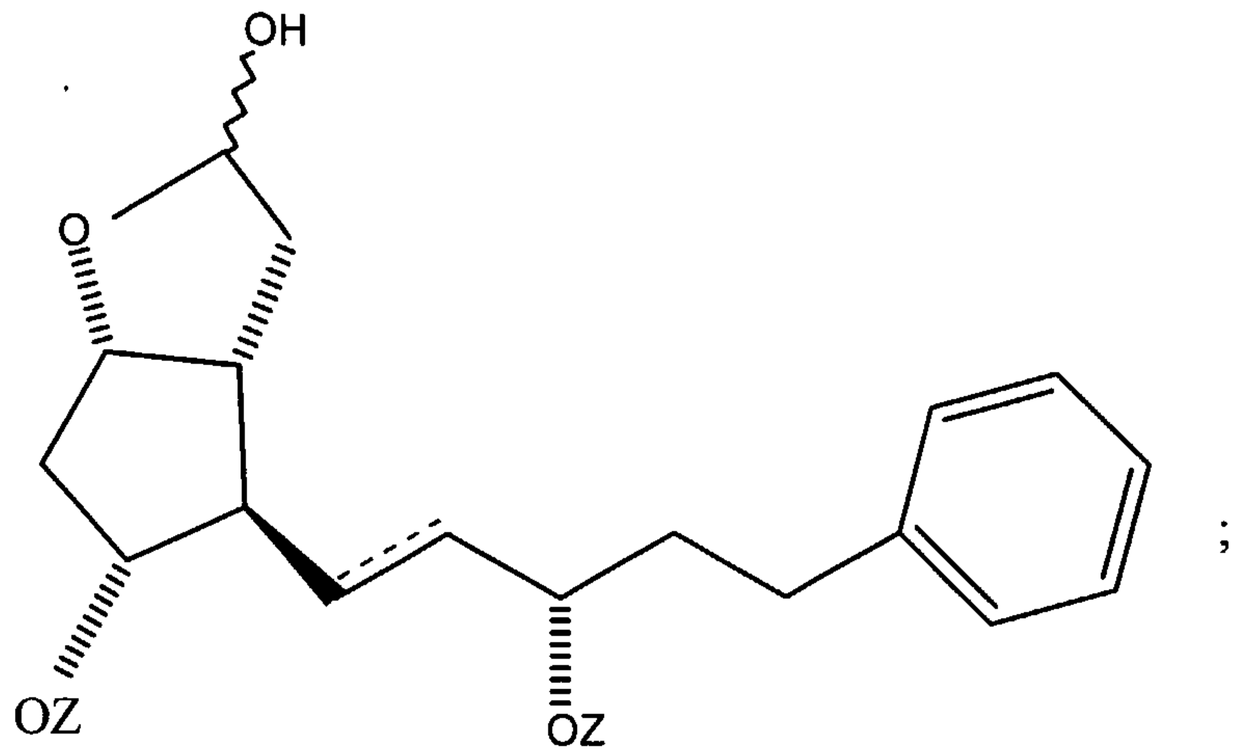
Preferably the present invention provides a process for the preparation of a prostamide which comprises the steps of

(b) reacting first intermediate having the general formula I




with DIBAL

wherein Z is a protecting group and the dotted line represents the presence or absence of a double bond to yield a second intermediate having the general Formula II

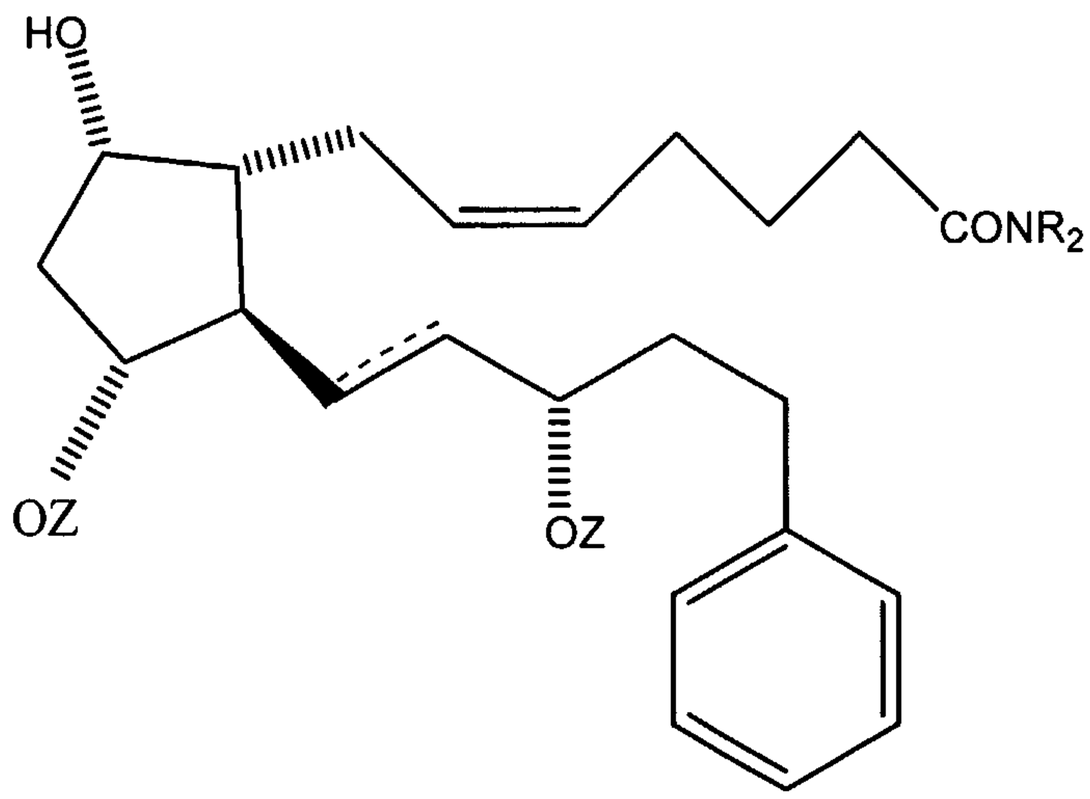



;

(b) reacting said second intermediate with

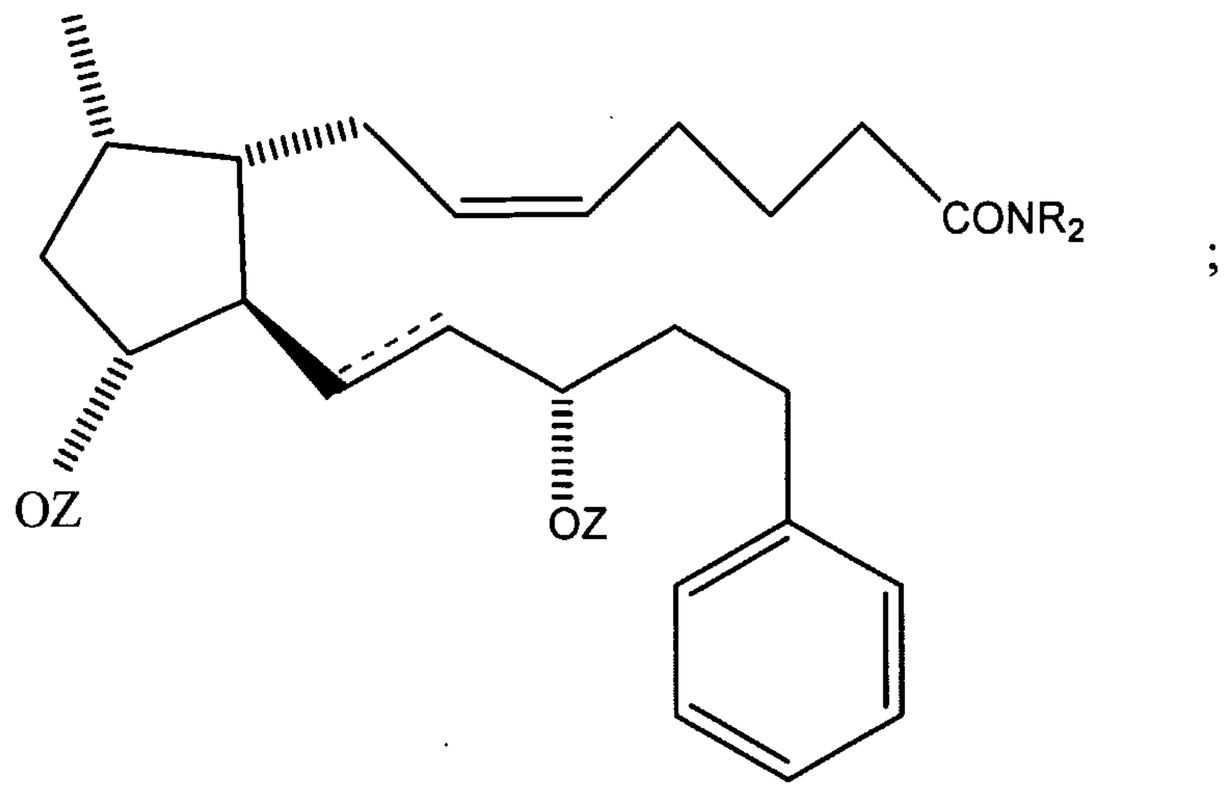
$Na(TMS)_2N$ and $Na(TMS)_2N$ and $(C_6H_5)_3P^+(CH_2)_6$ $CONR_2$ $X^-$

wherein R is a $C_1$-$_5$ alkyl or hydrogen and $X^-$ is an anion to yield a third intermediate having the general formula III



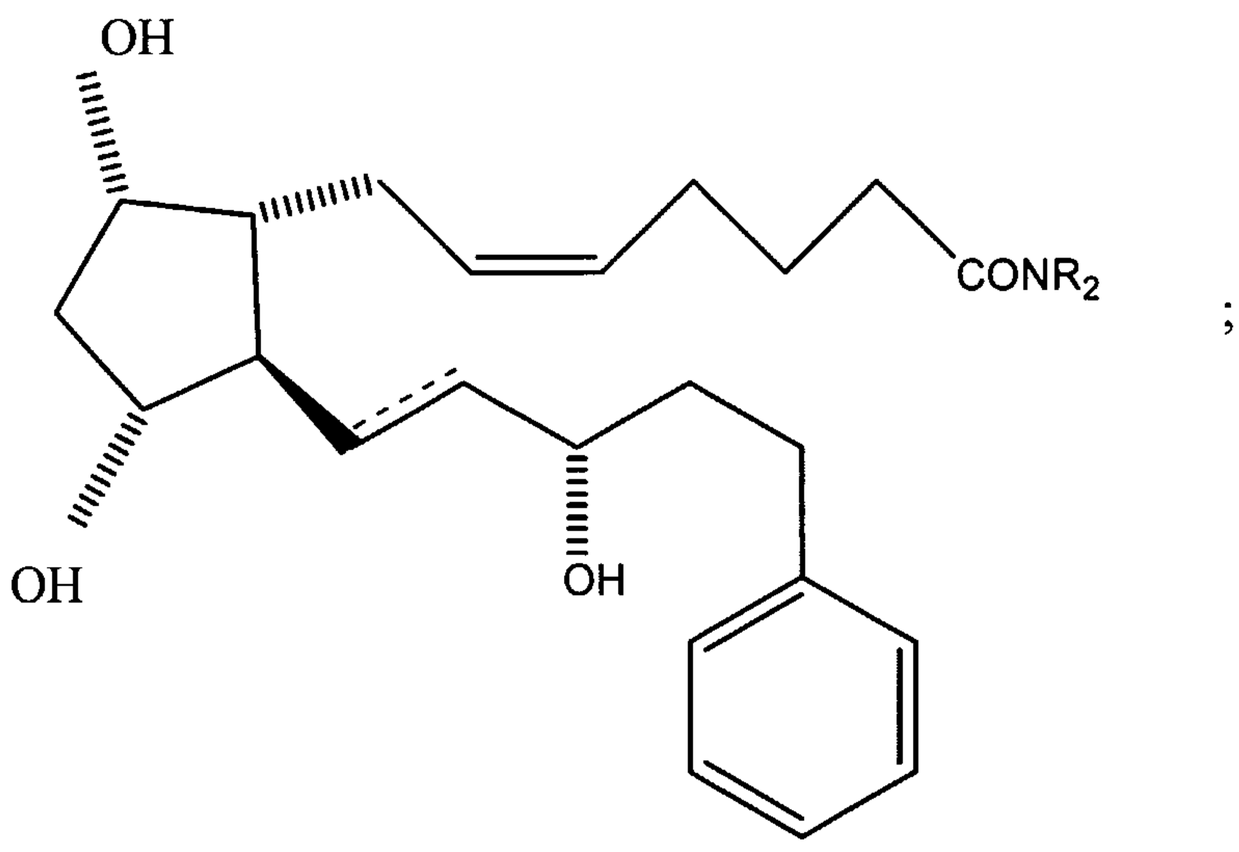

;

(c) reacting said third intermediate with TMSCl to yield a fourth intermediate having the general formula IV




;

(d) reacting said fourth intermediate to remove said protecting groups and yield a prostamide having the general formula V




;

More preferably at least one R is hydrogen and the other is ethyl.

More preferably Z is TMS.

More preferably step(d) comprises sequentially reacting said fourth intermediate with DMSO and aqueous LiCl.

DIBAL is disobutylaluminum hydride.

TMS is trimethylsilyl.

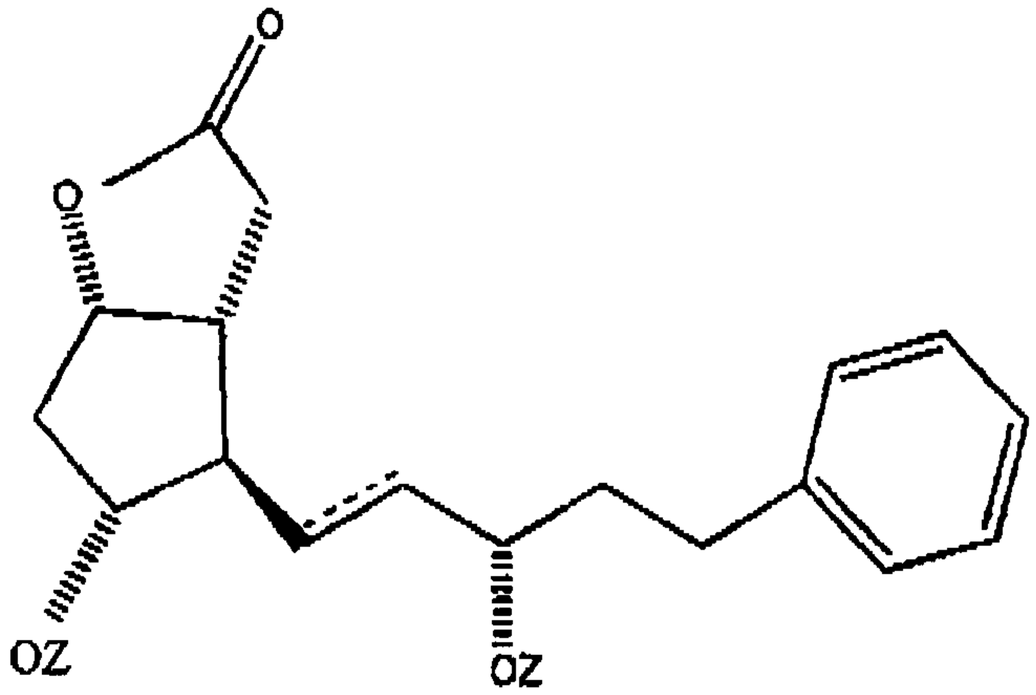
## DESCRIPTION OF THE PREFERRED EMBODIMENT

This step of the synthesis produces the crude bimatoprost API by introduction of the upper side chain. The lactone moiety is first reduced to the lactol under standard diisobutylaluminum hydride conditions. The lactol is not isolated, but is treated directly in situ with Wittig reagent. The crude bimatoprost is a mixture of cis and trans isomers about the 5,6-double bond. The cis isomer is the major project. The trans isomer is controlled in the crude bimatoprost specifications by a limit of NMT 8% on each individual impurity.

What is claimed is:

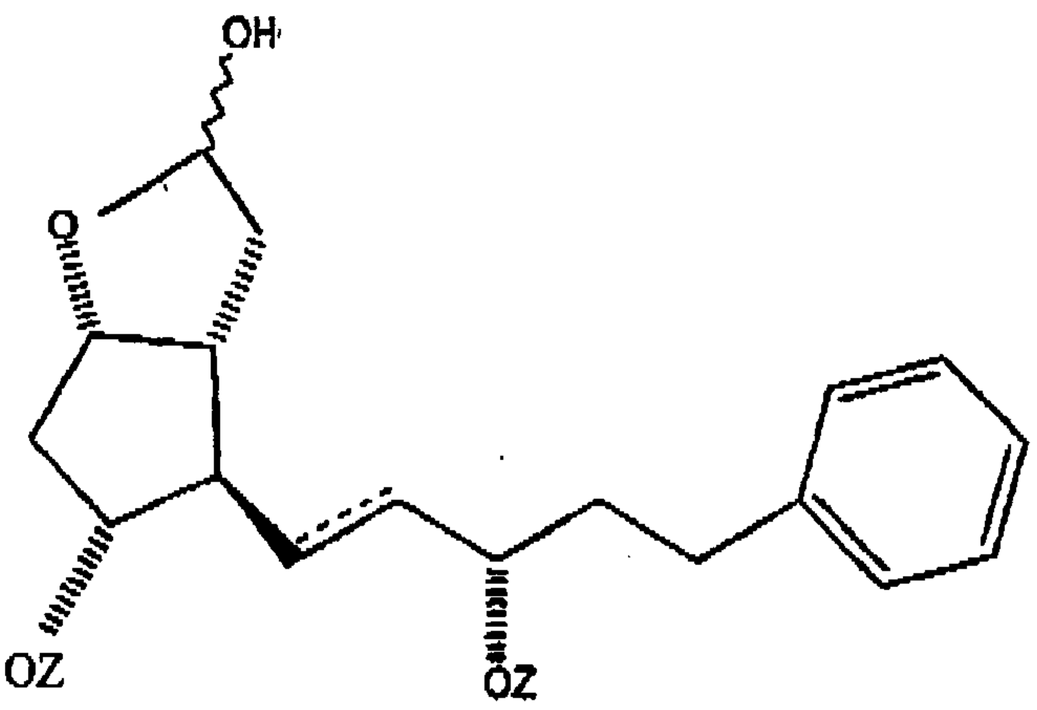
1. A process for the preparation of a prostamide which comprises the steps of

(a) reacting a first intermediate having the general formula I



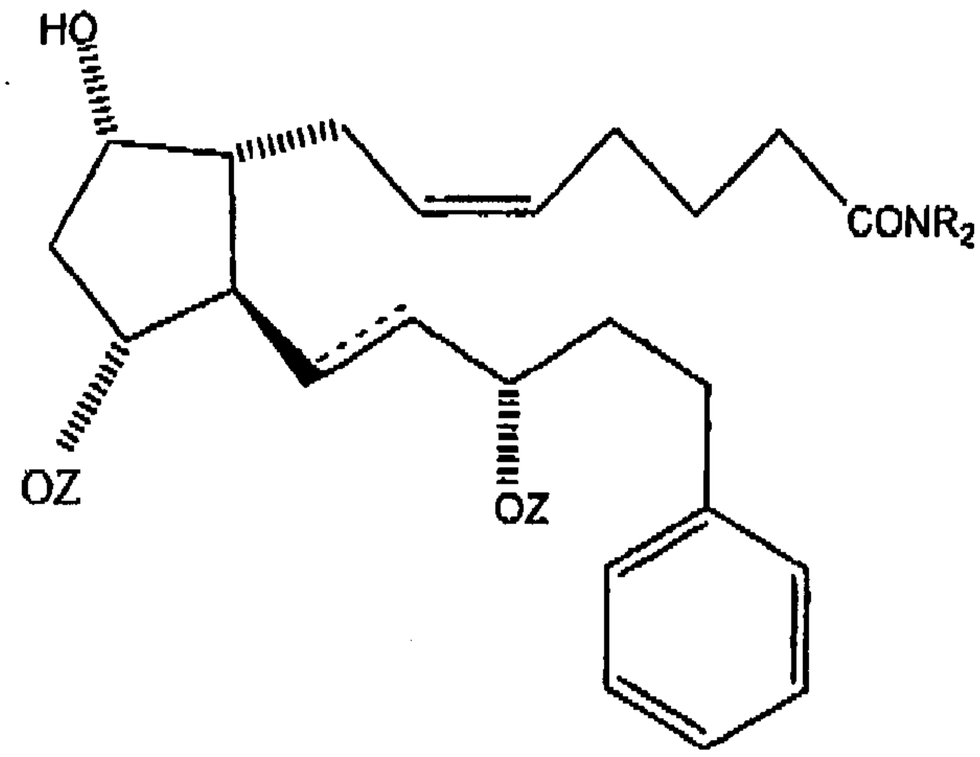

with DIBAL

wherein Z is a protecting group and the dotted line represents the presence or absence of a double bond to yield a second intermediate having the general Formula II



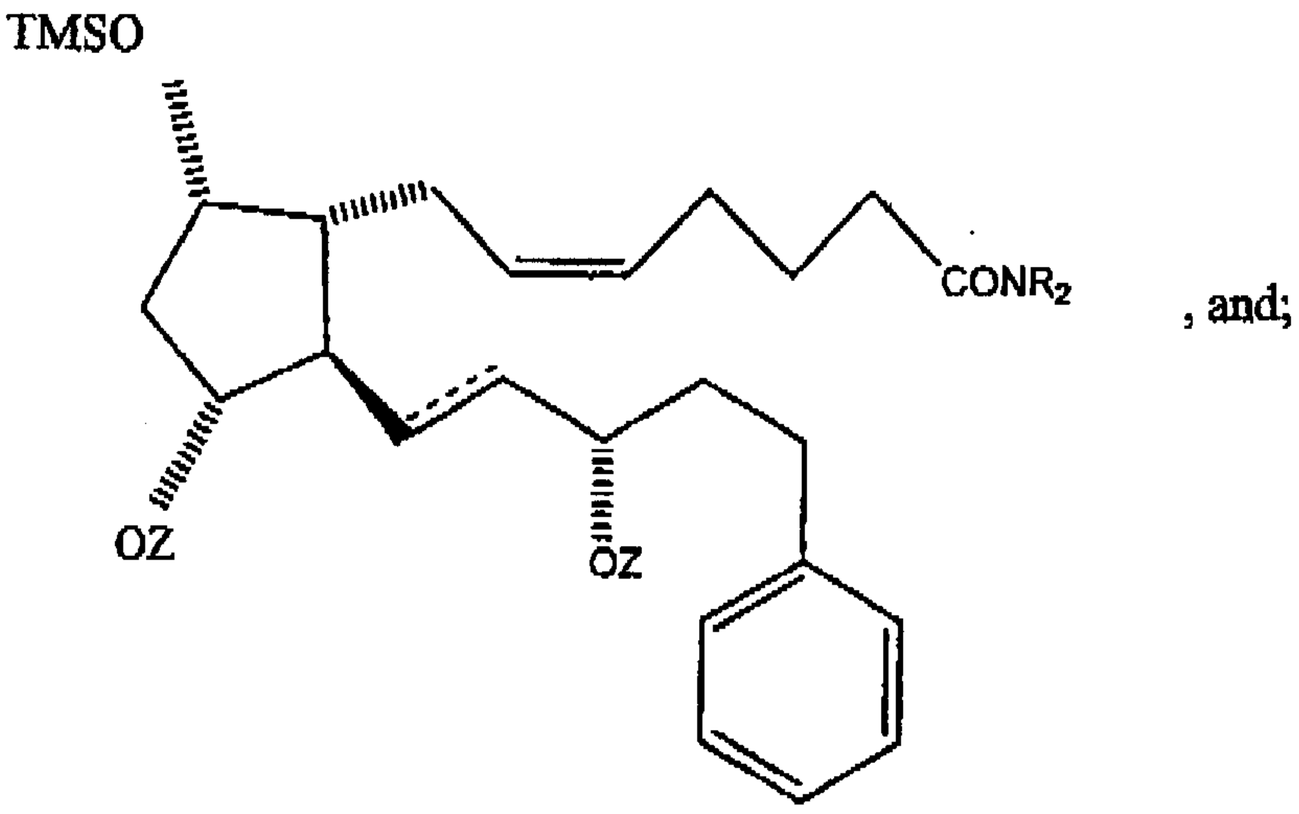

(b) reacting said second intermediate with $Na(TMS)_2N$ and $(C_6H_5)_3P^+(CH_2)_6\ CONR_2\ X^-$

wherein R is a $C_{1-5}$ alkyl or hydrogen and $X^-$ is an anion to yield a third intermediate having the general formula III



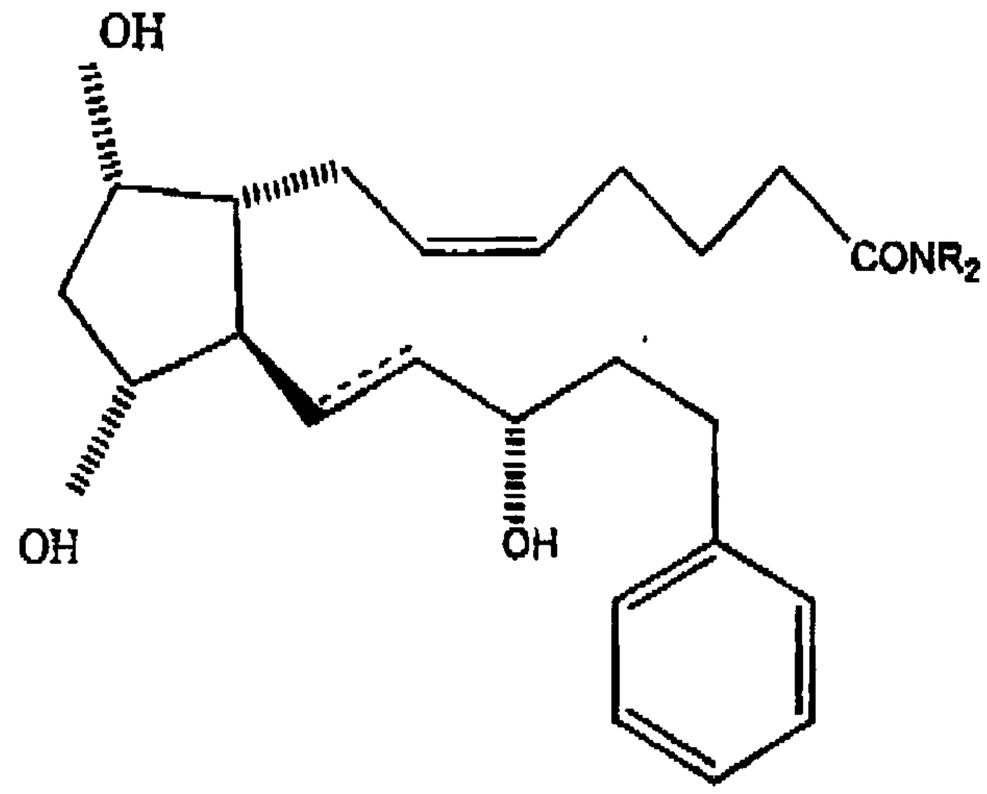

;

(c) reacting said third intermediate with a protecting agent TMSCl to yield a fourth intermediate having the general formula IV




, and;

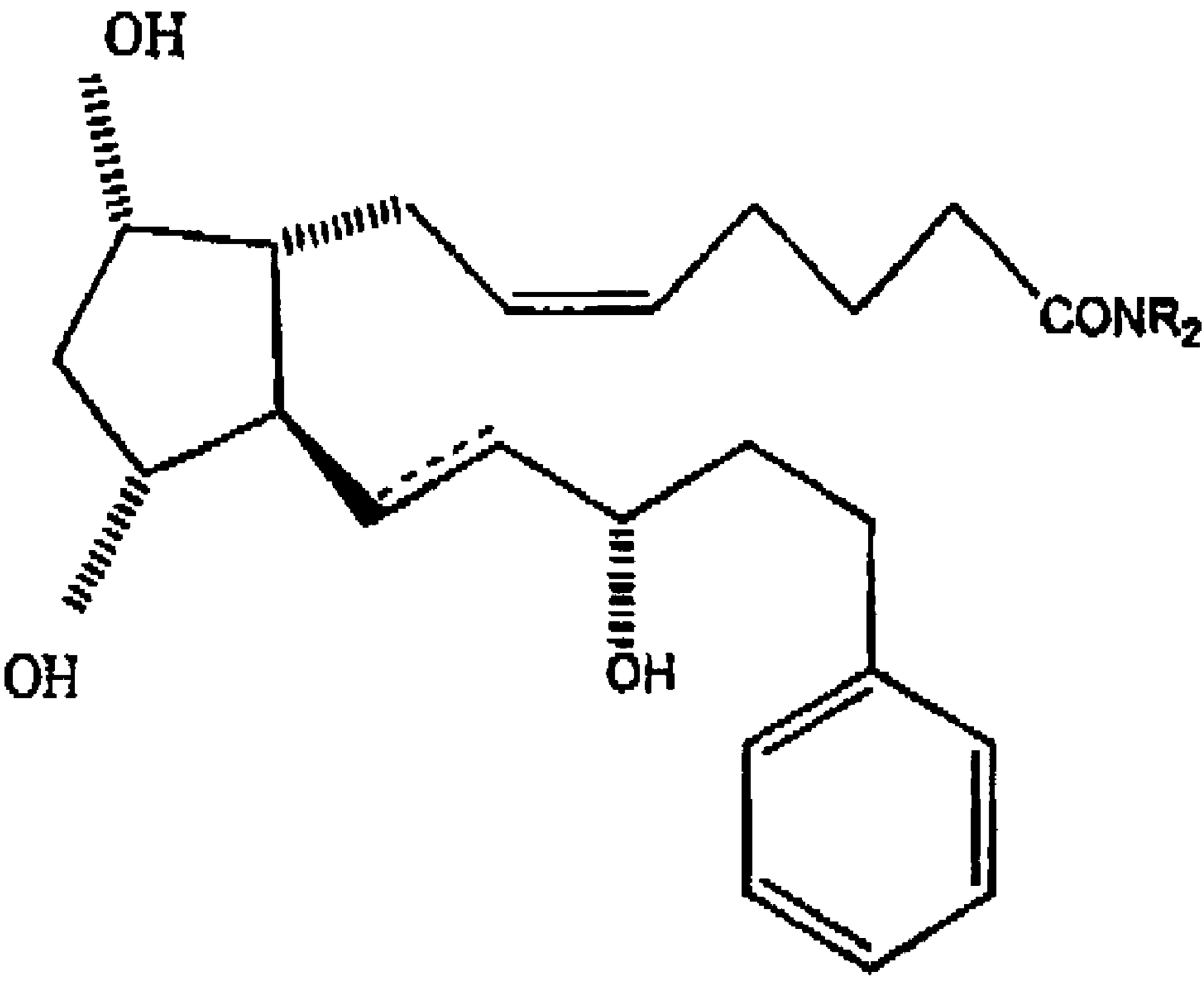
(d) reacting said fourth intermediate to remove said protecting groups and yield a prostamide having the general formula V




2. The process of claim 1 wherein one R is hydrogen and the other R is ethyl.

3. The process of claim 1 wherein Z is TMS.

4. The process of claim 1 wherein step (d) comprises sequentially reacting said fourth intermediate with DMSO and aqueous LiCl.


OH
CONR2
OH
OH